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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,110	02/24/2005	Qishou Xu	CU-4057 BWH	3549

26530 7590 09/08/2010

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EXAMINER	
GOON, SCARLETT Y	

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
09/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,110	XU ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8,12 and 21-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8,12 and 21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 21 July 2010 in which claims 22 and 24 have been amended to change the scope and breadth of the claims. No amendments to the claims were submitted.

The Declaration of Mr. Xu Qishou (inventor), submitted by Applicants on 21 July 2010 under 37 CFR § 1.132, is acknowledged and will be further discussed below.

Claims 1, 6-8, 12 and 21-34 are pending in the instant application and are examined on its merits herein.

Priority

This application is a National Stage entry of PCT/CN03/00609 filed on 29 July 2003 and claims priority to China foreign application 02125917.8 filed on 2 August 2002. A certified copy of the foreign priority document in Chinese has been received. No English translation has been received.

Rejections Withdrawn

Applicants' amendment and arguments, filed 21 July 2010, with respect to the rejection of claim 24 under 35 USC § 112, first paragraph, as failing to comply with the written description requirement, has been fully considered and is persuasive because the claim has been amended to replace the recitation "intermuscularly" with "intramuscularly," which is supported by the disclosure of the instant application. This rejection has been **withdrawn**.

A request for submission of additional data to support Applicants' arguments of unexpected results was discussed with Ms. Zareefa Flener, Applicants' attorney, on 17 August 2010. However, on 24 August 2010, Ms. Flener requested that the Examiner issue an Office Action which the Applicants will review. Ms. Flener indicated that Applicants would be interested in discussing the Office Action with the Examiner prior to submitting a response.

Since Applicants' arguments and Declaration, filed on 21 July 2010, are not sufficient to overcome the prior art rejections of record, as discussed below, the following rejections of record in the previous Office Action are maintained.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "CODPL" in claim 22 renders the claim herein indefinite. Acronyms or abbreviations can be interpreted differently depending on the context and the art. For example, "EPA" can stand for "eicosapentaenoic acid" or it can be an abbreviation for the "Environmental Protection Agency". Thus, it is unclear what "COPDL" is an abbreviation for, particularly since it is not readily apparent in the

Specification. To render the claim definite, it is respectfully suggested that Applicants spell out what they intend to claim (with sufficient support in the Specification), rather than use acronyms or abbreviations.

Response to Arguments

Applicants' amendment, filed 17 August 2010, with respect to the rejection of claim 22 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, has been considered but is not persuasive. It is noted that Applicants have amended claim 22 to expressly state that "CODPL" is "cyclophosphamide oncovin daunomycin prednione l-asparaginase." However, as the Specification does not clearly teach what CODPL is an abbreviation of, it is necessary that Applicants provide a prior art or reference to prove that CODPL is known in the art to represent the name they have added to claim 22.

The rejection is still deemed proper and therefore maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Section [0001]

Claims 1 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record).

Yamabe *et al.* teach the preparation of riboflavin trilaurate (abstract). It is noted that Yamabe *et al.* do not teach the positions of trilaurate esterification. However, based on the disclosed procedure, it is the Office's position that one of the esterified

positions is the 5'-OH as it is the only primary alcohol on the riboflavin chain, as compared to the remaining hydroxyl groups which are at a secondary position, and it is common knowledge to one of ordinary skill in the organic chemistry arts that a primary alcohol reacts much faster than secondary alcohols.

The teachings of Yamabe *et al.* differ from that of the instantly claimed invention in that Yamabe *et al.* teach a trilaurate ester of riboflavin whereas the claims of the instant invention is drawn to a 5'-laurate monoester of riboflavin.

Okuda *et al.* teach nutritional and ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate. To test the nutritional effects of the riboflavin derivatives, rats were fed either a standard diet, a riboflavin-deficient diet, a riboflavin-deficient diet supplemented with riboflavin-5'-monobutyrate suspended in olive oil, or a riboflavin-deficient diet supplemented with riboflavin-5'-monopalmitate suspended in olive oil (p. 9, under subheading "methods"). The authors previously showed that riboflavin tetrabutyrate had the same vitamin B_2 activity (nutritional and ariboflavinosis-curing effects) in young rats as riboflavin, but riboflavin tetrapalmitate did not have vitamin B_2 activity as rats administered riboflavin tetrapalmitate clearly showed ariboflavinosis. Similar to riboflavin tetrabutyrate, rats fed a diet supplemented with riboflavin-5'-monobutyrate exhibited vitamin B_2 activity (p. 13, second full paragraph). However, rats fed a diet supplemented with riboflavin-5'-monopalmitate showed signs of lower vitamin B_2 activity. Their results suggest that riboflavin-5'-monobutyrate is easily hydrolyzed to riboflavin, and hence has the same nutritional effect as riboflavin, while

riboflavin-5'-monopalmitate was only slowly hydrolyzed to riboflavin (p. 13, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B_2 activity as compared to riboflavin tetrabutyrate when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B_2 activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggest that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also

likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

Applicants are requested to note that the recitation "for intramuscular injection" in claim 34 is considered to be an "intended use" of the composition. The "intended use" of a composition will not further limit the claims drawn to a composition or product, so long as the prior art discloses the same composition comprising the same ingredients in an effective amount, as the instantly claimed. See, e.g., *Ex parte Masham*, 2 USPQ2d 1647 (1987) and *In re Hack* 114, USPQ 161.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 21 August 2010, and the Declaration of Mr. Xu Qishou, submitted by Applicants on 21 August 2010 under 37 CFR § 1.132, with respect to the rejections of record, maintained and re-stated in the instant Office Action, have been fully considered but are not persuasive.

Applicants maintain that Figures 4 and 5 of the Declaration of Mr. Qishou, submitted by Applicant on 12 January 2010 under 37 CFR § 1.132, clearly show that the 5'-laurate of riboflavin as claimed in the present invention has much better activity than that of the di-laurate or tri-laurate of riboflavin when intramuscularly administered. Therefore, Applicants argue that such an effect is hard to be derived or concluded from the prior art, and thus is not clearly obvious to a person skilled in the art. Applicants'

arguments and the Declaration of 12 January 2010 have been re-considered, but are still not persuasive. Although the highest curve in both Figures 4 and 5 are for 9010l, the monoester laurate compound, the results for the tri-laurate ester and the ester-free riboflavin compounds appear to be encompassed within the error bars of the monoester laurate compound. Thus, the results are not considered to be statistically significant. Furthermore, while it is noted that p-values have been provided to denote statistical significance, the results are observed only at specific weeks and not over the entire course of the time examined, thereby suggesting that over time, there is no statistical differences observed for better nutritional intake and effect between the different degrees of laurate esterificaton on riboflavin.

Applicants further submitted another Declaration on 21 July 2010 to argue that the claimed compound, compositions and methods are much less cytotoxic in comparison with other riboflavin ester derivatives, e.g. 5'-caprate or 5'-myristate of riboflavin. Applicants' arguments and the Declaration of Mr. Qishou, submitted on 21 August 2010, have been carefully considered but are not persuasive. Specifically, Applicants' argument of unexpected results is not commensurate in scope with the claimed subject matter. See MPEP § 716.02(d). More specifically, the claims are directed to a composition and a method of using the composition for treatment of various conditions, wherein the composition contains 50-150 mg of 5'-laurate riboflavin ester, 0.1-1mL of ethyl oleate and 0-1 mL of camellia oil. The minimum concentration of the claimed composition is 50 mg of 5'-laurate riboflavin ester in 1 mL of ethyl oleate and 1 mL of camellia oil (total volume of 2 mL). The 5'-laurate riboflavin ester has a

molecular weight of 558.67 g/mol, giving a minimum concentration of 44.7 mM. Applicants are requested to note that the Interview Summary dated 23 August 2010 incorrectly stated that the minimum concentration is 890 mM. At the maximum concentration of 150 mg of 5'-laurate riboflavin ester in 0.1 mL of ethyl oleate, the concentration is 2.68 M. The concentrations used for evaluation of cytotoxicity in the Declaration are 120 μmol/L and 240 μmol/L, which are significantly lower than the concentration of the claimed compositions and methods. Furthermore, claims 1 and 34 are merely drawn towards a compound and claim 6 is drawn to a composition comprising 5'-laurate riboflavin ester and ethyl oleate at any concentration. The showing of two concentrations, both in micromolar amounts, is not sufficient support that any and all concentrations of 5'-laurate riboflavin ester in ethyl oleate exhibit the argued unexpected results of lower cytotoxicity. Thus, Applicants' argument and showing of unexpected results in the Declaration are not commensurate in scope with the claimed invention.

Therefore, the Declarations of Mr. Xu Qishou is ineffective to rebut the *prima facie* case presented herein.

Applicants additionally argue that the bioavailability of the 5'-laurate of riboflavin is even higher than that of riboflavin when measured by weight gain after administration. This argument is not persuasive. This observation is considered *prima facie* obvious in view of the teachings of the prior art, and is therefore not considered to be unexpected. Furthermore, Applicants are requested to note that a showing of unexpected results

must be made in comparison with other mono-ester compounds and not ester-free riboflavin as the closest applied prior art discloses mono-ester compounds.

The rejection is still deemed proper and therefore maintained.

Section [0002]

Claims 6, 12, 23-26, 29, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in view of Remington: The Science and Practice of Pharmacy (of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.* and Okuda *et al.* differ from that of the instantly claimed invention in that they do not expressly disclose formulation of the riboflavin ester compositions with ethyl oleate.

Remington teaches that the goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration (p. 1660, column 1, paragraph 1). Different methods of drug delivery include conventional drug therapy and nonimmediate-release drug therapy, which includes delayed release, sustained release, site-specific release and receptor release (p. 1661, column 1, paragraph 1). Sustained-release systems

include any drug delivery system that achieves slow release of drug over an extended period of time (p. 1661, column 1, paragraph 30). Advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment (p. 1662, column 2, Table 1). The drug for sustained release may be formulated for oral or parenteral dosage. The most common types of dosage forms used for parenteral sustained-release drug therapy are intramuscular injections, implants for subcutaneous tissues and various body cavities and transdermal devices (p. 1669, column 2, subheading "Parenteral Dosage Forms"). Intramuscular injections may be in the form of aqueous solutions, complex formation, aqueous suspensions, and oil solutions or oil suspensions (p. 1670-1671). The rate-limiting step in drug release from an aqueous suspension is dissolution (p. 1670, column 1, subheading "Aqueous Suspensions"). In the case of oil solutions, the release rate of a drug is determined by partitioning of the drug out of the oil into the surrounding aqueous medium (p. 1670, column 2, subheading "Oil Solutions and Oil Suspensions"). Drug release from oil suspensions combines the principles involved in aqueous suspensions and oil solutions. The duration of action obtained from oil suspensions is longer than that from oil solutions (p. 1671, column 1, first full paragraph). Examples of oil solutions and oil suspensions are provided in Tables 10 and 11 wherein the oil component is from sesame oil or cottonseed oil (p. 1671).

The Goldenberg '740 patent teaches the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent. The biologically active agent is incorporated into a

polyol/thickened oil suspension, said biologically active agent in the form of a powder or aqueous solution, and said suspension capable of providing for the sustained-release of the biologically active agent (column 3, lines 41-47). The composition is prepared for parenteral administration to a warm blooded animal, wherein said suspension is administered subcutaneously, or intramuscularly, and the biologically active agent is released from the suspension at a controlled rate for up to one week or more (column 3, lines 48-54). The oils used in the composition are biocompatible, of low acidity, and essentially free from rancidity, and are selected from the group consisting of sesame seed, cannola, saffron, castor, cottonseed, olive, peanut, sunflower seed, ethyl oleate, vitamin E, and Miglyol 812 (column 6, lines 57-63).

Wicks *et al.* teach long-acting antiparasitic formulations of doramectin, suitable for injection. The formulation comprises 1-11% w/v of doramectin, in a solvent comprising castor oil at about 25-80% v/v and either (i) ethyl oleate at about 20-75% v/v, or (ii) fractionated coconut oil at about 20-75% v/v, and (iii) optional further auxiliaries (paragraphs 0005-0008). The said formulation has been shown to provide efficacy against economically important endo-parasites at up to 4 months, and ecto-parasites at up to 3 months, following a single injection (paragraph 0013).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various

methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate. Since Remington teaches that advantages of sustained release drug therapy are that it avoids patient compliance problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-5'-monolaurate compound, taught in the combined teachings of Yamabe *et al.* and Okuda *et al.*, into an oil suspension, such as with ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils, such as ethyl oleate, results in a prolonged release of the injectable suspension that would provide efficacy from up to one week to up to four months.

With regards to the limitation wherein the drug is administered to an animal that is a human, it is common practice in the pharmaceutical arts to first test drugs in animals, such as rats, before application to humans. Thus, successful *in vivo* testing in rats would marshal resources and direct the expenditure of effort to human clinical trials of the successful compounds, thereby providing an immediate benefit to the public.

This is considered to be analogous to the benefit provided by the showing that a drug has *in vivo* utility (see MPEP § 2107.01).

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 21 August 2010, and the Declaration of Mr. Xu Qishou, submitted by Applicants on 21 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 6, 12, 23-26, 29, 30 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, as applied to claims 1 and 34, further in view of Remington: The Science and Practice of Pharmacy, in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.*, in view of PG Pub No. US 2002/0142972 to Wicks *et al.*, have been fully considered but are not persuasive.

Applicants' arguments are the same as that presented under the subheading "Response to Arguments" in section [0001] above, and the Examiner's response is as presented therein.

Section [0003]

Claims 7, 8, and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above,

further in view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington; of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), as applied to 6, 12, 23-26, 29, 30, further in view of U.S. Patent No., 5,554,650 to Holl *et al.* (hereinafter referred to as the '650 patent; of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.* were as described in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.*, Remington, the Goldenberg '740 patent, and Wicks *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art do not expressly disclose a composition comprising the 5'-lauric acid ester of riboflavin with camellia oil, or a method of treating ariboflavinosis comprising administering the same composition.

The Holl '650 patent teaches an antiphlogistic, analgesic, antipyretic parenteral preparation comprising diclofenac, its salt, or both, a surfactant, cosurfactant, water, and optionally comprising an oily component, that can exhibit sustained therapeutic levels of diclofenac in plasma (column 1, lines 6-14, lines 60-67). Incorporation of an oily component in the parenteral preparation decreases the peak plasma concentration of diclofenac or its salt after administration, increases the time to achieve peak plasma concentration of diclofenac or its salt after administration, and prolongs the period of

time for which diclofenac or its salt remains active (column 3, lines 18-26). One or more oily components can be selected from the group consisting of glycerin fatty acid esters, fatty acid esters, and hydrocarbons (column 3, lines 27-30). Preferred are glycerin fatty acid esters that are almond oil, olive oil, sesame oil, peanut oil, fennel oil, camellia oil, corn oil, castor oil, cotton seed oil, and soybean oil, which may be used alone or in combination with one or more oily components (column 3, lines 34-41). The oily components may be incorporated into the parenteral preparation in an amount of about 0.5-30 wt%, preferably 1-15 wt% (column 3, lines 44-47).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of the Holl '650 patent, regarding incorporation of an oily component into a parenteral diclofenac preparation to prolong its period of activity after administration. Since Remington teaches that advantages of sustained release drug therapy are that it avoids patient compliance

problems, employs less total drug, and improves efficiency in treatment, one of ordinary skill in the art would have been motivated to formulate the riboflavin-5'-monolaurate compound, taught in the combined teachings of Yamabe *et al.* and Okuda *et al.*, into an oil suspension, such as with ethyl oleate, for sustained release, particularly since the duration of action obtained from oil suspensions is longer than that from oil solutions. Furthermore, as disclosed in the Goldenberg '740 patent and the teachings of Wicks *et al.*, formulation of a biologically active compound with oils such as ethyl oleate results in a prolonged release of the injectable suspension that would provide efficacy from up to one week to up to four months. Since the Holl '650 patent also teaches that oily components prolong the period at which an administered drug remains active, similar to Remington, the Goldenberg '740 patent, and Wicks *et al.*, and further teaches that the oily components can be used in combination with each other, one of ordinary skill in the art would have been further motivated to include additional oily components into the composition, with the expectation that the sustained delivery of the active drug would be maintained. Furthermore, as Remington teaches that the release rate of a drug in an oil solution is determined by partitioning of the drug out of the oil into the surrounding aqueous medium, and the release rate of a drug in an oil suspension is determined by the same factor as an oil solution as well as dissolution of the drug in an aqueous solution, one of ordinary skill in the art would conclude that the different properties of the oily components would affect the release rate of the drug, and thus, different combinations of the oily components, such as ethyl oleate and camellia oil, in different amounts, would also affect the release rate of the drug. As such, based on the

combined teachings of the prior art, one of ordinary skill in the art would be able to make various compositions of riboflavin-5'-monobutyrate in different oily components, in different concentrations, depending on the desired rate of drug release.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 21 August 2010, and the Declaration of Mr. Xu Qishou, submitted by Applicants on 21 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 7, 8, and 31-33 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, as applied to claims 1 and 34, further in view of Remington: The Science and Practice of Pharmacy, in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.*, in view of PG Pub No. US 2002/0142972 to Wicks *et al.*, as applied to 6, 12, 23-26, 29, 30, further in view of U.S. Patent No., 5,554,650 to Holl *et al.*, have been fully considered but are not persuasive.

Applicants' arguments are the same as that presented under the subheading "Response to Arguments" in section [0001] above, and the Examiner's response is as presented therein.

Section [0004]

Claims 21, 22 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington; of record), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; of record), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (of record), as applied to 6, 12, 23-26, 29, 30, further in view of PG Pub No. US 2003/0105104 A1 by Burzynski (of record), in view of journal publication by McCarthy *et al.* (of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.* were as described in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.*, Remington, the Goldenberg '740 patent, and Wicks *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art teach administration of riboflavin-5'-monolaurate for treatment of ariboflavinosis and not for the treatment of digestive tract catarrh caused by bone marrow transplantation, leukemia or chemotherapy.

Burzynski teaches a pharmaceutical composition comprising riboflavin, effectors of the urea cycle, and amino acids, suitably combined with appropriate carriers, diluents, or excipients (abstract; paragraph 0001 and 0008; claim 14), as well as a

method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy by administering the said composition to a cancer patient in need thereof (paragraph 0024; claim 1). Common side effects associated with cancer treatment include tiredness, loss of appetite, mucositis, diarrhea and myelosuppression (paragraph 0072). In example 1 (paragraphs 0070-0073), Burzynski shows that when a female patient diagnosed with adenocarcinoma of the colon was administered a composition comprising a sterile solution of six amino acids, L-arginine, and riboflavin prior to treatment by chemotherapy with methotrexate and 5-fluorouracil, the patient did not experience the side effects typically associated with the chemotherapy treatment.

McCarthy *et al.* teach risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract. Oral mucositis is a dose-limiting toxicity of 5-fluorouracil and includes inflammation and ulceration of the oral mucosa and myelosuppression (abstract; p. 484, column 2). Although no direct relationship could be drawn, their results suggest that a lower neutrophil count is associated with the development of oral mucositis during therapy (p. 488, column 2, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various

methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of Burzynski, regarding a pharmaceutical composition comprising riboflavin, effectors of the urea cycle and amino acids, with the teachings of McCarthy *et al.*, regarding the risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract catarrh. Since McCarthy *et al.* teach that as digestive tract catarrh is a risk factor of patients undergoing chemotherapy and Burzynski teach that riboflavin can alleviate the toxicity associated with a chemotherapy regimen, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the riboflavin compound taught by Burzynski with a riboflavin ester, such as riboflavin-5'-monolaurate, as taught in the combined teachings of Yamabe *et al.* and Okuda *et al.*, with the expectation that riboflavin-5'-monolaurate would treat digestive tract catarrh caused by chemotherapy. It is noted that the Burzynski reference does not specifically teach the administration of ester analogs of riboflavin to cancer patients exhibiting the common side effects of chemotherapy. However, as described above in section [0001] of the claim rejections under 35 USC § 103, Okuda *et al.* teach that esters of riboflavin can be hydrolyzed to the natural riboflavin compound and thus exhibit activity similar to riboflavin. Therefore, esters of riboflavin, such as the 5'-laurate monoester of riboflavin,

can serve as functional substitutes for natural riboflavin when administered in a composition. Furthermore, it would have *prima facie* obvious to one of ordinary skill in that art that the enhanced lipophilicity of the riboflavin ester due to the presence of the alkyl chain would enhance its migration through lipid bilayers of cells, and thus its bioavailability.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 21 August 2010, and the Declaration of Mr. Xu Qishou, submitted by Applicant on 21 August 2010 under 37 CFR § 1.132, with respect to the rejection of claims 21, 22 and 27 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, as applied to claims 1 and 34, further in view of Remington: The Science and Practice of Pharmacy, in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.*, in view of PG Pub No. US 2002/0142972 to Wicks *et al.*, as applied to 6, 12, 23-26, 29, 30, further in view of PG Pub No. US 2003/0105104 A1 by Burzynski (of record), in view of journal publication by McCarthy *et al.*, have been fully considered but are not persuasive.

Applicants' arguments are the same as that presented under the subheading "Response to Arguments" in section [0001] above, and the Examiner's response is as presented therein.

Section [0005]

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claims 1 and 34 above, further in view of Remington: The Science and Practice of Pharmacy (hereinafter referred to as Remington; PTO-892, Ref. U), in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.* (hereinafter referred to as the '740 patent; PTO-892, Ref. A), in view of PG Pub No. US 2002/0142972 to Wicks *et al.* (PTO-892, Ref. B), as applied to 6, 12, 23-26, 29, 30, further in view of U.S. Patent No. 6,565,891 to Chandra (herein referred to as the '891 patent, of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington, the Goldenberg '740 patent, and Wicks *et al.* were as described in section [0002] above of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.*, Remington, the Goldenberg '740 patent, and Wicks *et al.* differ from that of the instantly claimed invention in that the combined teachings of the prior art teach administration of riboflavin-5'-monolaurate for treatment of ariboflavinosis and not for the treatment of persistent oral ulcer.

The Chandra '891 patent teaches a nutritional supplement for children that is most effective in optimizing health, increasing the immunity, and decreasing the instances and severity of infection, particularly among children (abstract). The

importance of each of the component vitamins and minerals making up the nutritional supplement is described in detail. Of particular relevance, is the importance of riboflavin in the nutritional supplement. The Chandra '891 patent teaches that riboflavin participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain (column 7, lines 22-31). It is used therapeutically to ameliorate ariboflavinosis resulting from diverse causes such as inadequate dietary intake, decreased assimilation, rare genetic defects in the formation of specific flavoproteins, hormonal disorders and after use of certain drugs. Symptoms indicating riboflavin deficiency include rough skin, angular stomatitis, cracked lips, and mouth ulcers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the various methods of drug delivery and the advantages of sustained drug delivery, with the teachings of the Goldenberg '740 patent, regarding the preparation of polyol/thickened oil suspensions containing a biologically active agent, for the sustained delivery of the biologically active agent, with the teachings of Wicks *et al.*, regarding long-acting antiparasitic formulations of doramectin, suitable for injection, comprising doramectin, in a solvent comprising castor oil or ethyl oleate, with the teachings of the Chandra '891 patent, regarding the various symptoms of riboflavin deficiency. Since the Chandra '891

patent teaches that oral ulcers are a symptom of riboflavin deficiency, it is the Office's position that the patient population being treated for ariboflavinosis with a riboflavin ester would necessarily overlap with the patient population that has oral ulcers, and thus would be treated using the same methods.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

Applicants' arguments, filed 21 August 2010, and the Declaration of Mr. Xu Qishou, submitted by Applicant on 21 August 2010 under 37 CFR § 1.132, with respect to the rejection of claim 28 under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.*, in view of journal publication by Okuda *et al.*, as applied to claims 1 and 34, further in view of Remington: The Science and Practice of Pharmacy, in view of U.S. Patent No. 6,245,740 B1 to Goldenberg *et al.*, in view of PG Pub No. US 2002/0142972 to Wicks *et al.*, as applied to 6, 12, 23-26, 29, 30, further in view of U.S. Patent No. 6,565,891 to Chandra, have been fully considered but are not persuasive.

Applicants' arguments are the same as that presented under the subheading "Response to Arguments" in section [0001] above, and the Examiner's response is as presented therein.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/SCARLETT GOON/
Examiner
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